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EXAMINER	
DUFFY, BRADLEY	
ART UNIT	**PAPER NUMBER**
1643	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	04/12/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/508,978	HWU ET AL.	
	Examiner	Art Unit	
	Brad Duffy	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 January 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5,8,11-22,25,28-38 and 57-63* is/are pending in the application.

4a) Of the above claim(s) *1-5,8,11-22,25,28-38,57,58 and 60-63* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *59* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *24 September 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *9/24/04, 2/25/05, 6/9/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *Notice to comply*.

DETAILED ACTION

1. The preliminary amendment filed September 24, 2004, is acknowledged and has been entered. Claims 5, 11-13, 22, 28-30 and 35 have been amended. Claims 6-7 and 23-24 have been canceled. Claims 39-57 are newly added.

2. The preliminary amendment filed July 19, 2005, is acknowledged and has been entered. Claims 58-65 are newly added.

3. The amendment filed January 18, 2007, is acknowledged and has been entered. Claims 2, 3, 15, 16, 19, 20, 59, and 63 have been amended. Claims 9-10, 26-27, 39-56 and 64-65 have been canceled.

4. The election with traverse filed January 18, 2007, is acknowledged and has been entered.

Applicant has elected the invention of Group XXIII, claim 59, drawn to a method of inducing apoptosis of a natural killer cell comprising contacting the NK cell with an IL-21 polynucleotide.

5. Claims 1-5, 8, 11-22, 25, 28-38 and 57-63 are pending in the application.

6. Claims 1-5, 8, 11-22, 25, 28-38, 57-58 and 60-63 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim.

7. Claim 59 is under examination.

Request to Change Inventorship under 37 CFR 1.48(c)

8. In view of the papers filed July 19, 2005, it has been found that this nonprovisional application has been amended to claim previously unclaimed subject matter that was invented by inventors not named in the application, as originally filed. Therefore, since the inclusion of these inventors was necessitated by amendment of the claims and the error occurred with any deceptive intent by these inventors, the inventorship of this application has been corrected in compliance with 37 CFR 1.48(c). The inventorship of this application has been changed by the addition of Warren Leonard, Rosanne Spolski and Katsutoshi Ozaki.

Election/Restrictions

9. Applicant's traversal of the restriction and election requirement set forth in the Office action mailed September 18, 2006, is acknowledged.

Applicant's arguments have been carefully considered but have not been found persuasive for the following reasons:

The traversal is on the grounds that, "the inclusion of more than one invention is permitted if all inventions are so linked as to form a single general inventive concept (MPEP § 1893.03(d))" and that WO 99/61617, which discloses the administration of IL-21 polypeptides to patients to treat neoplasia, is a non-enabling reference.

Contrary to Applicant's assertions, all[1] of the claimed inventions are not linked so as to form a single general inventive concept for the reasons set forth in the Office action mailed September 18, 2006. Notably, PCT Rule 13.2 does not require that the prior art have an enabling disclosure, and therefore WO 99/61617 has not been reviewed by the examiner to determine if that is the case. M.P.E.P. § 1850 states: "Whether or not any particular technical feature makes a "contribution" over the prior art, and therefore constitutes a "special technical feature," should be considered with respect to **novelty and inventive step**" alone (emphasis added), and not with respect to any requirement set forth under 35 U.S.C. § 112, first paragraph.

Furthermore, in response to applicant's argument that, at the very least, groups XXII and XXIII should be examined together because both groups now comprise contacting a natural killer cell with an IL-21 polypeptide, the inventions of Groups XXII and XXIII do not share the same or corresponding special technical feature. Although presently both claims 58 and 59 recite a process comprising contacting a NK cell with an IL-21 polypeptide, at the time of the restriction, claim 59 did not and was an independent claim; and nonetheless, the special technical feature of the invention of claim 59 was and still remains the induction of apoptosis of a NK cell by contacting the cell with a polynucleotide encoding the IL-21 polypeptide, whereas the special technical feature of the invention of claim 58 is and always has been the induction of apoptosis of a NK cell by contacting the cell with the polypeptide. Thus, the inventions are materially different processes comprising different process steps, which therefore necessarily induce the apoptosis of a NK cell by different modes of action or effect, so as to lack unity of invention and form a single general inventive concept.

Accordingly the restriction between the inventions of Groups XXII and XXIII is deemed proper.

Finally, applicant has argued that the restriction of individual claims into separate groups is improper, citing MPEP 803.02, further arguing that there would not be a serious burden to examine these claims as required under MPEP 803. This argument

[1] Underlining added for emphasis

is not found persuasive as this is a national stage application filed under 35 USC 371 and therefore restriction practice is governed by PCT Rule 13. Notably, PCT Rule 13.3 states that

> The determination whether a group of inventions is so linked as to form a single general inventive concept shall be made without regard to whether the inventions are claimed in separate claims or as alternatives within a single claim[2].

In the instant case each treatment for cancer comprising either an IL-21 polypeptide alone or in any combination with a vaccine, an antigen-specific T lymphocyte or a cytokine does not have unity of invention as required by PCT Rule 13 because they are not so linked as to form a single general inventive concept for the reasons set forth in the Office action mailed September 18, 2006. For example, each method of treating cancer would be expected to have different criteria for success and would require the measurement of different correlations to determine if the particular method could actually treat cancer and therefore has a different special technical feature. Finally, unity of invention restriction practice for national stage applications does not require that there be a serious search burden when making a lack of unity of invention requirement (see MPEP 1893.03(d)).

Therefore, for these reasons and the reasons set forth in the Office action mailed September 18, 2006, these inventions do not share unity of invention as required under PCT Rule 13 and the restriction/election requirement is deemed proper and therefore made FINAL.

Information Disclosure Statement

10. The references cited in the information disclosure statements filed on September 24, 2004, February 25, 2005 and June 9, 2005, have been considered except for the GenBank Accession Nos listed as documents AI-AM. Notably, it cannot be ascertained when these particular sequences referred to by these Accession Nos were publicly

[2] Underlining added for emphasis

available, so these references were crossed out because they fail to comply with 37 CFR § 1.98 (b)(5).

Priority

11. Applicant's claim under 35 USC §§ 119 and/or 120 for benefit of the earlier filing date of the 60/368438, filed March 27, 2002, is acknowledged.

However, claim 59 does not properly benefit under 35 U.S.C. §§ 119 and/or 120 by the earlier filing dates of the priority document claimed, since written support for the instant claim, drawn to a method of inducing apoptosis, is not be found in the provisional application.

To receive benefit of the earlier filing date under §§ 119 and/or 120, the later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application); the disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

Accordingly, the effective filing date of the claims is deemed the filing date of PCT/US03/09707, namely March 23, 2003.

Specification

12. The disclosure is objected to because of the following informalities:

a. The specification is objected to because the use of improperly demarcated trademarks has been noted in this application. Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner that might adversely affect their validity as trademarks. See MPEP § 608.01(v).

Examples of such improperly demarcated trademarks appearing in the specification are StatView™ and CellTiter 96™ (see, e.g., page 23 and 28).

Appropriate correction is required. Each letter of a trademark should be capitalized or otherwise the trademark should be demarcated with the appropriate symbol indicating its proprietary nature (e.g., ™, ®), and accompanied by generic terminology. Applicants may identify trademarks using the "Trademark" search engine under "USPTO Search Collections" on the Internet at http://www.uspto.gov/web/menu/search.html.

b. The disclosure is objected to for the following reason: The specification contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. § 1.821(a)(1) and (a)(2). Sequences appearing in the specification and/or drawings must be identified by sequence identifier in accordance with 37 C.F.R. 1.821(d). According to 37 CFR § 1.821(a), an unbranched sequence of four or more specifically identified amino acids or an unbranched sequence of ten or more nucleotides must be identified by sequence identification numbers. See MPEP § 2422.01.

In this instance, paragraph [0003] on page 1 of the specification discloses the following amino acid sequence, "WSXWS" that is not identified by sequence identification number. Therefore, since this amino acid sequence contains an unbranched sequence with four specifically identified amino acids it requires a sequence identification number pursuant to 37 CFR § 1.821(a). Notably, this sequence also does not appear in the sequence listing as filed.

As noted in the attached Notice to Comply, appropriate action correcting this deficiency is required. If necessary to correct the deficiency, Applicant must submit paper and computer-readable copies of a substitute sequence listing, together with an amendment directing its entry into the specification and a statement that the content of both copies are the same and, where applicable, include no new matter.

c. The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is

requested in correcting any errors of which applicant may become aware in the specification.

Appropriate correction is required.

Claim Objections

13. Claim 59 is objected to as improperly depending upon a claim directed to a non-elected invention, i.e., claim 58.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

14. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

15. Claim 59 is indefinite because it uses the term "IL-21" as the sole means for identifying the polypeptide encoded by the polynucleotide to which the claims are directed. The use of laboratory designations to identify a particular molecule renders the claims indefinite because different laboratories may use the same nomenclature to identify distinct molecules. For example, a search of "IL-21" in the protein database available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=Protein, conducted on March 28, 2007, provided 78 possible IL-21 proteins and it is unclear to which one(s) the claim refer. Accordingly, it is submitted that the claims fail to delineate the metes and bounds of the subject matter that Applicant regards as the invention with the requisite clarity and particularity to permit the skilled artisan to know or determine infringing subject matter.

16. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

17. Claim 59 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

This is a "written description" rejection.

The considerations that are made in determining whether a claimed invention is supported by an adequate written description are outlined by the published Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, para. 1, ``Written Description" Requirement (Federal Register; Vol. 66, No. 4, January 5, 2001). A copy of this publication can be viewed or acquired on the Internet at the following address: <http://www.gpoaccess.gov/>.

In the instant case, claim 59 is drawn to a genus of "polynucleotides" that encode "IL-21" polypeptides, variants thereof, or fragments of such polypeptides or variants, which, presumably when expressed in natural killer cells, induce the cells to undergo apoptosis. However, the written description in this case only sets forth one species of "polynucleotide", i.e., the murine IL-21 plasmid comprising the murine interleukin 21 polynucleotide (see page 4, description of Figure 6 and page 24, example 1) that was cloned with murine IL-21 primers consisting of SEQ ID NO:3 and SEQ ID NO:4 and that induces apoptosis of natural killer cells when injected into mice.

The specification on page 6 discloses that,

> "Nucleic acid molecule" or "polynucleotide," as used herein, refers to any oligonucleotide or nucleotide sequence, fragments or portions of either of the foregoing, which encode all or part of IL-21. The nucleic acid molecule or polynucleotide can be DNA or RNA of either genomic or synthetic origin, which can be single- or double-stranded, and can be a coding (sense) or non-coding (anti-sense) strand. By way of non-limiting example, fragments can be nucleic acid sequences that are greater than 10-60 nucleotides in length, and preferably include fragments that are at least 61-100 nucleotides, or which are 101 nucleotides or greater in length."

and

> "an IL-21 amino acid sequence" or "IL-21 polypeptide" as used herein refers to an IL-21 oligopeptide, peptide, polypeptide, or protein sequence, and fragments or portions thereof, that are naturally occurring or are synthetic. Amino acid sequence fragments or portions thereof can be from about 5 to about 30 amino acids, preferably from about 5 to about 15 amino acids in length. Such fragments and portions [0026] Similarly, "an IL-21 amino acid sequence" or "IL-21 polypeptide" as used herein refers to an IL-21 oligopeptide, peptide, polypeptide, or protein sequence, and fragments or portions thereof, that are naturally occurring or are synthetic. Amino acid sequence fragments or portions thereof can be from about 5 to about 30 amino acids, preferably from about 5 to about 15 amino acids in length. Such fragments and portions desirably retain the biological activity or function of the IL-21 polypeptide"

Later on page 7 the specification discloses that,

> A "variant" of the IL-21 polypeptide refers to an amino acid sequence that is altered by one or more amino acids. The variant can have "conservative" changes, wherein a substituted amino acid has similar structural or chemical properties, e.g., replacement of leucine with isoleucine. More rarely, a variant can have "non-conservative" changes, such as, for example, replacement of a glycine with a tryptophan. Minor variations can also include amino acid deletions or insertions, or both.

Thus, the claims are broadly, but reasonably interpreted as encompassing an extremely large genus of structurally and functionally diverse polynucleotides that can induce apoptosis of natural killer cells, that do not necessarily retain any structural or functional similarity to the particularly described murine interleukin 21 polynucleotide besides their ability to induce apoptosis in natural killer cells. Therefore, written description of the present application only reasonably conveys one "polynucleotide", i.e. the murine IL-21 plasmid comprising the murine interleukin 21 polynucleotide that was cloned with murine IL-21 primers consisting of SEQ ID NO:3 and SEQ ID NO:4 and that induces apoptosis of natural killer cells when injected into mice as a polynucleotide that induces apoptosis of natural killer cells because the specification does not describe the structure of a sufficient number of species of the genus of "polynucleotides" that are encompassed by the disclosure of the specification to reasonably convey to the skilled artisan that Applicant had possession of the claimed invention at the time the application was filed.

The description of one "polynucleotide" that encodes an IL-21 polypeptide, variant or fragment, i.e. the murine IL-21 plasmid comprising the murine interleukin 21 polynucleotide that induces apoptosis of natural killer cells when injected into mice, is not representative of the entire genus because the genus is highly variable, inclusive to

a variety of structurally undefined "polynucleotides" that also are functionally diverse beyond their requirement of inducing apoptosis. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. Clearly, one of skill in the art would not immediately envisage the genus of "polynucleotides" encompassed by the claims or recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the single disclosed "polynucleotide" that encodes an IL-21 polypeptide, variant or fragment and that induces apoptosis of natural killer cells.

Further, it is not sufficient to define a substance solely by its principal biological property, because an alleged conception having no more specificity than that is simply a wish to know the identity of any material with that biological property. Per the *Enzo* court's example, (*Enzo Biochem, Inc. v. Gen-Probe Inc.*, 63 USPQ2d 1609 (CA FC 2002) at 1616) of a description of an anti-inflammatory steroid, i.e., a steroid (a generic structural term) couched "in terms of its function of lessening inflammation of tissues" which, the court stated, "fails to distinguish any steroid from others having the same activity or function". Similarly, the function of inducing apoptosis of natural killer cells does not distinguish any "polynucleotide", from others having the same activity or function and as such, fails to satisfy the written-description requirement. Applicant has not disclosed any relevant, identifying characteristics, such as structure or other physical and/or chemical properties, sufficient to show possession of the claimed genus. Mere idea or function is insufficient for written description; isolation and characterization at a minimum are required. A description of what a material does, rather than what it is, usually does not suffice. *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406.

Structural features that could distinguish polynucleotides that encode an IL-21 polypeptide, variant or fragment and that induce apoptosis of natural killer cells are missing from the disclosure and the claims. No common structural attributes identify the members of the genus. The general knowledge and level of skill in the art do not supplement the omitted description, because specific, not general guidance is needed. Since the disclosure does not describe the common attributes or structural

characteristics that identify members of the genus, and because the genus is highly variant, the function of inducing apoptosis of natural killer cells alone is insufficient to describe the genus of "polynucleotides" that encode an IL-21 polypeptide, variant or fragment. One of skill in the art would reasonably conclude that the disclosure of a single polynucleotide that encodes an IL-21 polypeptide, variant or fragment, does not provide a representative number of species of all such polynucleotides that would be sufficient to describe the claimed genus.

The Federal Circuit has decided that a patentee of a biotechnological invention cannot necessarily claim a genus after only describing a limited number of species because there may be unpredictability in the results obtained from species other than those specifically enumerated. See *Noelle v. Lederman*, 69 USPQ2d 1508 1514 (CA FC 2004) (citing *Enzo Biochem II*, 323 F.3d at 965; *Regents*, 119 F.3d at 1568). In this instance, while the specification describes the structure of one polynucleotide that encodes an IL-21 polypeptide that can induce apoptosis of natural killer cells, one cannot predict what structure is common to all such polynucleotides.

"[G]eneralized language may not suffice if it does not convey the detailed identity of an invention." *University of Rochester v. G.D. Searle Co.*, 69 USPQ2d 1886 1892 (CAFC 2004). Here, there is no language that adequately describes the genus of "polynucleotides" to which the claims are directed.

Again, the genus of "polynucleotides" as encompassed by the claims does not share a disclosed common structural feature that relates to their stated function of inducing apoptosis of natural killer cells.

Given the lack of particularity with which the "polynucleotides", to which the claims are directed, are described in the specification, it is submitted that the skilled artisan could not immediately envision, recognize or distinguish at least most of the members of the genus of "polynucleotides" to which the claims are directed; and therefore the specification would not reasonably convey to the skilled artisan that Applicant had possession of the claimed invention at the time the application was filed.

18. Claims 1-15 and 48-51 are rejected under 35 U.S.C. 112, first paragraph, because the specification, **while being enabling for using** a method for inducing apoptosis of murine natural killer cells *in vivo*, said method comprising contacting said natural killer cells with a plasmid comprising the murine interleukin 21 polynucleotide that was cloned with murine IL-21 primers consisting of SEQ ID NO:3 and SEQ ID NO:4, wherein said polynucleotide induces apoptosis of said natural killer cells, **does not reasonably provide enablement for using** a method for inducing apoptosis of natural killer cells in humans or other species and **does not reasonably provide enablement for using** any other methods encompassed by the claims that read on "gene therapy" (i.e., the *in vivo* delivery of genetic information to targeted cells within a body using naked DNA or viral vectors or by reintroducing *ex vivo* modified host cells into the body, so as to achieve clinical or therapeutic effect). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The amount of guidance, direction, and exemplification disclosed in the specification, as filed, would not be sufficient to enable the skilled artisan to use the claimed invention at the time the application was filed without undue experimentation.

MPEP § 2164.01 states:

> The standard for determining whether the specification meets the enablement requirement was cast in the Supreme Court decision of *Mineral Separation v. Hyde*, 242 U.S. 261, 270 (1916) which postured the question: is the experimentation needed to practice the invention undue or unreasonable? That standard is still the one to be applied. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). Accordingly, even though the statute does not use the term "undue experimentation," it has been interpreted to require that the claimed invention be enabled so that any person skilled in the art can make and use the invention without undue experimentation. *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988).

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue". These factors, which have been outlined in the Federal Circuit decision of *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), include, but are not limited

to, the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed. See also *Ex parte Forman*, 230 USPQ 546 (BPAI 1986).

As the claim is specifically directed to methods comprising contacting natural killer cells with a polynucleotide to induce apoptosis and the specification discloses that the polynucleotides of the invention can be used for treatment of diseases in humans (see pages 11, 12 and 14), the claim reads on processes termed in the art as "gene therapy".

The art of gene therapy, i.e., the *in vivo* delivery of genetic information to targeted cells within a human body using naked DNA or viral vectors or by reintroducing *ex vivo* modified host cells into the human body, is still in its infancy. Moreover, the art is highly unpredictable and its successful application has been hindered by numerous limitations, which the specification does not remedy and would preclude the skilled artisan from having a reasonable expectation of successfully making and using the claimed invention without undue experimentation.

For example, the teachings of the specification have not overcome the problems with *in vivo* delivery and expression. Verma et al. (*Nature* 1997, **389**: 239-242) teach that the Achilles heel of gene therapy is gene delivery (page 239, column 3). Verma et al. state that the ongoing problem is the inability to deliver genes efficiently and to obtain sustained expression; see entire document (e.g., page 239, column 3). In this case the specification teaches that more that 2/3 of the expression of mIL-21 in mice is lost after 3 days (see Figure 1) and does not address how to obtain sustained expression in mice or humans. Similarly, Amalfitano et al. (*Current Gene Therapy* 2002, **2**: 111-133) teach that non-viral mediated transfer of DNA generally suffers from low transduction efficiencies; see entire document (e.g., page 111, column 2). In addition, Amalfitano et al. discuss numerous limitations that have been encountered in using retroviral vectors to deliver DNA into a subject and teaches the use of adenoviral vectors can be

ineffective because of the induction of strong immune responses in the host to the viral vectors and direct acute and chronic toxicity caused by the vector itself; see entire document (e.g., abstract).

It is noted that Amalfitano et al. teach that a despite general lack of success, the first conclusive evidence that gene therapy can show efficacy in humans was achieved in human X-linked SCID subjects *via* retrovirus transduction (page 111, column 2). However, since this publication, The Department of Health and Human Services has released a memorandum dated January 14, 2003, a copy of which is attached to this Office action, that urges all such investigations to be discontinued until new data are available, the possible etiology and risks of adverse events associated are considered, and recommendations emerge. Despite the initial promise of the trial studying gene transfer as a possible treatment for the disease, investigators have found that retroviral-mediated insertion of the transgene has caused the subjects to develop cancer. The results of the trial underscore the high degree of unpredictability associated with the art and the fact that the skilled artisan could not make or use the claimed invention without undue and/or unreasonable experimentation.

The state of the art, as a whole, is well defined by Pandha et al. (*Current Opinion in Investigational Drugs* 2000; **1** (1): 122-134). Pandha et al. teach:

> Despite the rapid technological advances that continue to sustain the field of cancer gene therapy, few individual patients have benefited from the revolution so far. The plethora of clinical trials described confirms that each malignancy will have its own ideal strategy based on the associated molecular defects, and there has been rapid progress from this viewpoint. At the same time, there has been a renewed appreciation for the limitations to gene therapy, which include low efficiency of gene transfer, poor specificity of response and methods to accurately evaluate responses, and lack of truly tumor-specific targets at which to aim. As with all new therapies, we are climbing a steep learning curve in terms of encountering treatment-related toxicities, as well as profound ethical and regulatory issues (abstract).

Furthermore, in this case, Wang et al (Cancer Research, 63:9016-9022, 2003) teach that it is highly unpredictable whether a gene delivery method of a IL-21 polynucleotide would be practical in the clinic, i.e, for treatment of humans (see entire document, e.g., page 9021, right column, second full paragraph).

Finally, it appears that there are fundamental differences in murine natural killer cells when compared to human natural killer cells, so it would be highly unpredictable if

IL-21 polynucleotides, fragments or variants from one species would induce apoptosis in natural killer cells from another species, or even if a human IL-21 polynucleotide would induce apoptosis in human natural killer cells. For example, Parrish-Novak et al (J. Leukoc. Biol., 72:856-863, 2002) teach that IL-21 causes different effects in human natural killer cells that it does in mouse natural killer cells and that one explanation for this difference in natural killer response to IL-21 is that natural killer cells in laboratory mice are relatively naïve compared to human natural killer cells because human natural killer cells are exposed to significantly more environmental antigens. Thus, one of skill in the art would not conclude that results obtained in a mouse system using the murine IL-21 polynucleotide would extrapolate to using any IL-21 polynucleotide, fragments or variants to induce apoptosis in natural killer cells from other species and would have to practice undue experimentation to practice the invention commensurate in scope with the claims.

In conclusion, upon careful consideration of the factors used to determine whether undue experimentation is required, in accordance with the Federal Circuit decision of *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the amount of guidance, direction, and exemplification disclosed in the specification, as filed, is not deemed sufficient to have enable the skilled artisan to use the claimed invention at the time the application was filed without undue and/or unreasonable experimentation.

Conclusion

19. No claims are allowed.

20. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brad Duffy whose telephone number is (571) 272-9935. The examiner can normally be reached on Monday through Friday 7:00 AM to 4:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Respectfully,
Brad Duffy
571-272-9935

bd
March 28, 2007

LARRY R. HELMS, PH.D.
SUPERVISORY PATENT EXAMINER

Notice to Comply	Application No. 10/508,978	Applicant(s) HWU ET AL.	
	Examiner Brad Duffy	Art Unit 1643	

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

Applicant must file the items indicated below within the time period set the Office action to which the Notice is attached to avoid abandonment under 35 U.S.C. § 133 (extensions of time may be obtained under the provisions of 37 CFR 1.136(a)).

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825 for the following reason(s):

☒ 1. This application clearly fails to comply with the requirements of 37 C.F.R. 1.821-1.825. Applicant's attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990). If the effective filing date is on or after July 1, 1998, see the final rulemaking notice published at 63 FR 29620 (June 1, 1998) and 1211 OG 82 (June 23, 1998).

☐ 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 C.F.R. 1.821(c).

☐ 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 C.F.R. 1.821(e).

☐ 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 C.F.R. 1.822 and/or 1.823, as indicated on the attached copy of the marked -up "Raw Sequence Listing."

☐ 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A Substitute computer readable form must be submitted as required by 37 C.F.R. 1.825(d).

☐ 6. The paper copy of the "Sequence Listing" is not the same as the computer readable from of the "Sequence Listing" as required by 37 C.F.R. 1.821(e). The correct SEQ ID NO:2 is present in the paper copy of the of the sequence listing only. Therefore a search of the correct sequence is not possible.

☒ 7. Other: In this instance, paragraph [0003] on page 1 of the specification discloses the following amino acid sequence, 'WSXWS' that is not identified by sequence identification number. Furthermore, this sequence does not appear in the sequence listing as filed.

Applicant Must Provide:

☒ An initial or substitute computer readable form (CRF) copy of the "Sequence Listing".

☒ An initial or substitute paper copy of the "Sequence Listing", **as well as an amendment specifically directing its entry into the application**.

☒ A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

For questions regarding compliance to these requirements, please contact:

For Rules Interpretation, call (703) 308-4216 or (703) 308-2923
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